



King's Research Portal

DOI:

[10.1016/j.jad.2017.07.028](https://doi.org/10.1016/j.jad.2017.07.028)

Document Version

Peer reviewed version

[Link to publication record in King's Research Portal](#)

Citation for published version (APA):

Hidalgo-Mazzei, D., Reinares, M., Mateu, A., Jururena, M. F., Young, A. H., Pérez-Sola, V., Vieta, E., & Colom, F. (2017). Is a SIMPLe smartphone application capable of improving biological rhythms in bipolar disorder? *Journal of Affective Disorders*, 223, 10-16. <https://doi.org/10.1016/j.jad.2017.07.028>

Citing this paper

Please note that where the full-text provided on King's Research Portal is the Author Accepted Manuscript or Post-Print version this may differ from the final Published version. If citing, it is advised that you check and use the publisher's definitive version for pagination, volume/issue, and date of publication details. And where the final published version is provided on the Research Portal, if citing you are again advised to check the publisher's website for any subsequent corrections.

General rights

Copyright and moral rights for the publications made accessible in the Research Portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognize and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from the Research Portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain
- You may freely distribute the URL identifying the publication in the Research Portal

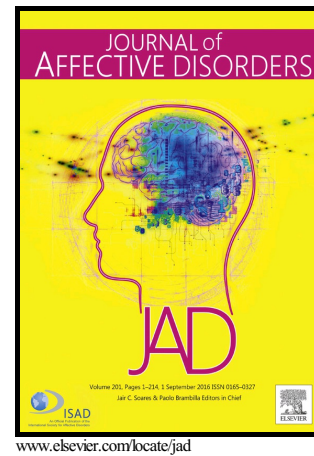
Take down policy

If you believe that this document breaches copyright please contact librarypure@kcl.ac.uk providing details, and we will remove access to the work immediately and investigate your claim.

Author's Accepted Manuscript

Is a SIMPLe smartphone application capable of improving biological rhythms in bipolar disorder?

Diego Hidalgo-Mazzei, María Reinares, Ainoa Mateu, Mario F. Jururena, Allan H. Young, Víctor Pérez-Sola, Eduard Vieta, Francesc Colom



PII: S0165-0327(17)30646-8
DOI: <http://dx.doi.org/10.1016/j.jad.2017.07.028>
Reference: JAD9094

To appear in: *Journal of Affective Disorders*

Received date: 28 March 2017
Revised date: 2 June 2017
Accepted date: 8 July 2017

Cite this article as: Diego Hidalgo-Mazzei, María Reinares, Ainoa Mateu, Mario F. Jururena, Allan H. Young, Víctor Pérez-Sola, Eduard Vieta and Francesc Colom, Is a SIMPLe smartphone application capable of improving biological rhythms in bipolar disorder?, *Journal of Affective Disorders* <http://dx.doi.org/10.1016/j.jad.2017.07.028>

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting galley proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Is a SIMPLE smartphone application capable of improving biological rhythms in bipolar disorder?

Diego Hidalgo-Mazzei, MD, PhD ^{1,2}, María Reinares, PsyD, PhD ¹, Ainoa Mateu, DClinPsy ³, Mario F. Jururena, MD, PhD ^{2,4}, Allan H. Young, MD, PhD ², Víctor Pérez-Sola, MD, PhD ^{5,6}, Eduard Vieta, MD, PhD ^{1*}, Francesc Colom, PsyD, PhD ⁶,

¹Bipolar Disorder Program, Department of Psychiatry and Psychology, Institute of Neuroscience, Hospital Clinic, University of Barcelona, IDIBAPS, CIBERSAM, Barcelona, Catalonia, Spain.

²Centre for Affective Disorders, Institute of Psychiatry, Psychology & Neuroscience, King's College London, United Kingdom.

³Centre for Psychiatry, Division of Brain Sciences, Department of Medicine, Imperial College London, London, United Kingdom.

⁴Stress and Affective Disorder Programme, Department of Neuroscience and Behaviour, University of Sao Paulo, Brazil.

⁵Institute of Neurosciences and Addictions, Hospital del Mar, Barcelona, Catalonia, Spain

⁶Mental Health Group, IMIM-Hospital del Mar, CIBERSAM, Barcelona, Catalonia, Spain.

***Correspondence to:** Eduard Vieta, Bipolar Disorders Program, Neurosciences Institute, Hospital Clínic de Barcelona, IDIBAPS, CIBERSAM, Universitat de Barcelona, Villarroel 170, 08036. Barcelona, Catalonia, Spain. Tel. (34) 93 227 54 00. Fax. (34) 93 227 92 28. E-mail: evieta@clinic.ub.es

Abstract

Background

Biological rhythms (BR) disturbance has been suggested as a potential mediator of mood episodes in Bipolar Disorder (BD). The Biological Rhythms Interview of Assessment in Neuropsychiatry (BRIAN) was designed as an assessment tool to evaluate BR domains comprehensively. In the context of a trial evaluating a smartphone application delivering personalized psychoeducational contents for BD

(SIMPLe 1.0), the main aim of this study is to evaluate the potential impact of SIMPLe 1.0 in BR regulation using the BRIAN scale.

Methods

51 remitted BD patients were asked to use the application for 3 months. Paired t-test analyses were employed to compare baseline and follow-up BRIAN's total and domains scores. The sample was divided into completers and non-completers of the study to evaluate differences between groups regarding BRIAN scores using ANCOVA analyses.

Results

The BRIAN's mean total score of the whole sample significantly decreased from baseline to post-intervention (35.89 (SD 6.64) vs. 31.18 (SD 6.33), $t=4.29$, $p=0.001$). At post-intervention, there was a significant difference between groups regarding the total BRIAN mean score (29.47 (SD 6.21) completers vs. 35.92 (SD 3.90) non-completers, $t=2.50$, $p=0.02$). This difference was maintained after conducting a one-way ANCOVA controlling for pre-intervention BRIAN scores, $F(1, 46)=10.545$, $p=0.002$.

Limitations

A limited sample, pre-post measures, and a short study timeframe could have affected the results. Additional factors affecting BR, such as medication, could not be ruled out.

Conclusion

Our results suggest that there are potential positive effects of a psychoeducational smartphone application as an adjunctive to treatment as usual on BD patients' BR.

List of abbreviations

ANCOVA, Analysis of Covariance; BD, Bipolar disorder; BRIAN, Biological Rhythms Interview of Assessment in Neuropsychiatry; BT, Biological Rhythms; HDRS, Hamilton depression rating scale; IPSRT, Interpersonal and social rhythm therapy ; MG, Morisky Green test; NES, Not elsewhere specified ; SD, Standard deviation; SIMPLe, Signs and Symptoms Self-monitoring and Psychoeducation in Bipolar Patients with a Smart-phone Application Project; SRT, Social Rhythms therapies ; YMRS, Young mania rating scale; TAU, Treatment as usual

Keywords: Bipolar disorder; Biological rhythms; Psychoeducation; Smartphone.

Introduction

Bipolar disorder (BD) is a chronic recurrent condition affecting approximately 2% of the world population (Grande et al., 2016; Merikangas et al., 2011). Alongside the acute episodes, the illness encompasses a significant negative impact on the quality of life, cognition and life expectancy of those affected (Angst et al., 2002; Kessing et al., 2015; Martínez-Arán et al., 2004; Michalak et al., 2005).

Biological rhythms disturbance has been suggested as a potential mediator not only of the mood episodes but also of the impairment and reduced quality of life in BD patients (Ashman et al., 1999; Giglio et al., 2010; Murray and Harvey, 2010; Rosa et al., 2013; Shen et al., 2008). Previous studies reported that biological rhythm disturbance was proportional to the intensity of depressive

symptoms in BD, and both variables contributed to a poorer psychosocial functioning (Pinho et al., 2016). Variations of the biological rhythms are widely recognized as one of the most common warning signs in BD, being part of the diagnostic criteria for mood episodes (American Psychiatric Association, 2013; Harvey et al., 2009). However, until recently, there has been a lack of well validated instruments available to correctly assess this issue. The Biological Rhythms Interview of Assessment in Neuropsychiatry (BRIAN) was designed as an assessment tool to ascertain most of the biological rhythms' domains (i.e. sleep/wake cycles, social activity and diet intake). It has been validated in different countries and languages, and extensively employed with the aim of evaluating biological rhythms in BD (Giglio et al., 2009; Moro et al., 2014; Rosa et al., 2013).

Accordingly, the disturbance of biological rhythms has been addressed by evidence-based psychotherapeutic interventions in the field of BD. Improving habits regularity is, very likely, one key factor in order to understand the proven efficacy of psychoeducation in BD (Cardoso et al., 2015; Colom and Vieta, 2006). Not by chance, each and every psychological intervention tested in the field of BD includes lifestyle one way or another. Particularly, Interpersonal and Social Rhythm Therapy (IPSRT) and other Social Rhythms therapies (SRTs) have targeted biological rhythms with some encouraging results (Frank, 2007; Frank et al., 2005; Haynes et al., 2016).

Unfortunately, there are several barriers hampering psychological treatments' broad implementation and availability (Colom, 2011; Reinares et al., 2014; Stafford and Colom, 2013). It is assumed that the vast majority of bipolar patients worldwide do not have access to a proper psychotherapeutic treatment.

Internet-based resources may improve the accessibility and affordability of psychological treatments for the whole affected population. Interestingly, people diagnosed with BD often use internet to gather information about their condition (Bauer et al., 2016). Hence, there is an increasing number of initiatives aimed to adapt psychotherapeutic treatments to Internet platforms (Hidalgo-Mazzei et al., 2015a). Most of them, attempted to provide psychoeducational contents and programs over web-based platforms, showing high levels of feasibility but mixed results regarding its efficacy (Hidalgo-Mazzei et al., 2016).

On the other hand, the rising use of smartphones has further enhanced the potential to ubiquitously and unobtrusively track behaviour and mood (Gershon et al., 2016; Glenn and Monteith, 2014). This is especially relevant since, in recent years, a great percentage of socializing activities have shifted from "traditional in-person" to online social networks, nowadays mostly centred on smartphones (Morahan-Martin and Schumacher, 2003; Sarwar and Rahim Soomro, 2013).

Despite these advancements, very few of the current smartphone applications (i.e. app) developed for BD routinely assess sleep and most of them cover a small percentage of psychoeducational contents, revealing an overall poor evidence-based quality (Nicholas et al. 2015). The SIMPLE project main aim is to provide mood monitoring and personalized psychoeducation contents through a smartphone app. The psychoeducational contents cover all the modules of evidence-based psychoeducational programs. Furthermore, content related to sleep/wake cycles was especially emphasized both in the app monitoring and psychoeducational messages (Hidalgo-Mazzei et al. 2015b). The central purpose of the SIMPLE app, as an adjunctive to treatment as usual, is to promote BD patients' self-management and empowerment in order to modify behaviours and prevent relapses alongside quality of life improvement. The feasibility and satisfaction of the first

version of the SIMPLE 1.0, relying solely on the use of the app and subjective information, was evaluated in a 3-month feasibility trial which has shown 74% retention rates (Hidalgo-Mazzei et al. 2016b).

In the context of this trial, the main aim of this study is to evaluate the impact of the SIMPLE app on biological rhythms regulation.

Methodology

The intervention SIMPLE 1.0

Overall, the SIMPLE 1.0 app consists of a daily short 5-item screening test, where the user has to reply by means of a visual friendly slider to his/her state regarding current mood, energy, irritability, night-sleep duration and medication intake. This daily assessment is completed once a week with a more comprehensive YES or NO test, considering all DSM-5 criteria for manic and depressive episodes including –and paying special attention to– suicidal thoughts. Based on this collected information, a daily pop-up notification prompts the user to read a short psychoeducational message. The time to fulfil the daily tests and to receive psychoeducational messages could be configured by the user as well as the day of the week to do the weekly test. Psychoeducational messages are based on an evidence-based group psychoeducation program (Colom and Vieta, 2006) and other client-aimed materials produced by the Bipolar Disorder Group at Hospital Clinic of Barcelona. These educational messages provide the user with a brief information or advice of how to deal with specific situations to avoid a relapse. Each message is extracted from a library of more than 500 messages categorized according to different clinical situations. The application's algorithm selects which category should be targeted based on the users' answers (e.g. if adherence problems

are identified, the educational message will focus on this issue). One of those categories is specifically aimed to tackle circadian rhythms and sleep disturbances.

Procedure, participants and measures

The feasibility study evaluating the first version of the app was conducted from March 2015 to June 2015 as part of the broader SIMPLe project. The sample (N=51) consisted of a consecutive sample of remitted BD patients to whom it was requested to use the application. The eligibility criteria included a diagnosis of a BD type I, II or not elsewhere specified (NES) based on DSM-5 criteria. The study was approved by the Ethics Committee of the Hospital Clínic of Barcelona and registered at clinicaltrials.gov (Identifier: NCT02258711).

Sociodemographic data and results of clinical assessments were collected during the study. The following clinical measures were administered in face-to-face interviews at baseline and after 3 months of the app use: the Spanish validated versions of the Young Mania Rating Score (YMRS)(Colom et al., 2002; Young et al., 1978) and 17-item Hamilton Depression Rating Score (HDRS)(Hamilton, 1960; Ramos-Brieva and Cordero-Villafila, 1988), 4-item Morisky-Green test (MG) (Morisky et al., 1986) and the BRIAN –validated Spanish version- (Giglio et al., 2009; Rosa et al., 2013). The BRIAN is a 21-item evaluation considering five main areas of daily rhythms (i.e. sleep, activities, social rhythms, eating patterns and predominant circadian rhythms). Each item is scored using an ordinal 4-points scale according to the frequency of daily habits disturbance, ranging from 1 for never to 4 for often. The total BRIAN score is the sum of all individual items scores. Thus higher scores suggest a greater degree of rhythms disturbance (Giglio et al., 2009).

Additionally, the use of the application as well as the input of subjective data was analysed from the data stored at the cloud server during the duration of the study. Detailed baseline characteristics of the sample, the app design process and the results of the feasibility study are described in detail elsewhere (Hidalgo-Mazzei et al., 2016, 2015b).

Statistical analyses

An assessment of normality was previously performed to determine the distribution of the variables implicated in the analyses. Accordingly, paired t-test analyses were employed to compare baseline and follow-up BRIAN's domains and total scores. We further divided the group in completers and non-completers according to whether they had used the application for the 3-month period or abandoned it before the conclusion of the study. In order to evaluate differences between both groups regarding BRIAN scores, paired t-test and ANCOVA analyses were performed. Other clinical variables changes and app use parameters, which could possibly affect the BRIAN scores, were evaluated as well using Wilcoxon signed-rank test, Pearson's correlations, and multiple regression and ANCOVA analyses. Statistical significance was established at $p = < .05$ level. All analyses were two-tailed and carried out using SPSS version 23.0.

Results

The Shapiro-Wilk test for the BRIAN scores showed not statically significant results ($p=0.17$) which led to assume the normality of its distribution. The BRIAN's mean total score of the whole sample significantly decreased before and after the intervention (35.89 (SD 6.64) vs. 31.18 (SD 6.33), $t=4.29$, $p=0.001$). Amongst the BRIAN's domains, all of them but the activities score ($p=0.071$) were significantly reduced ($p<0.05$).

The baseline sociodemographic and clinical variables divided by completers and non-completers are presented in Table 2. A t-test for independent samples was conducted to compare relevant baseline clinical variables (i.e. previous episodes, years since diagnosis) between both groups, showing no statistical significant differences. After recruitment, two patients never activated or used the application, thus these cases were left out of the analyses. At baseline, there were not significant differences regarding total BRIAN mean score among the group of completers and non-completers (35.28 (SD 6.96) vs. 37.62 (SD 5.53), $t=0.36$, $p=0.73$). At follow-up, there was a significant difference between both groups regarding the total BRIAN mean score (29.47 (SD 6.21) completers vs. 35.92 (SD 3.90) non-completers, $t=2.50$, $p=0.02$). In order to determine the statistically significant difference between groups on post-intervention BRIAN total scores controlling for pre-intervention baseline scores, we conducted a one-way ANCOVA. After a Levene's test and normality checks ensured that assumptions were met, the results confirmed the significant differences between groups on the final score, $F(1, 46)= 10.545$, $p=0.002$.

We further explored the relations of the BRIAN post intervention scores with the app usage parameters. We found significant correlations between this score and the frequency of weekly interaction with the app ($r=-0.45$, $p=0.01$), the number of weekly tests completed ($r=-0.49$, $p=0.01$) and sleep time reported ($r=-0.50$, $p=0.01$). It is relevant to mention that the daily test mood score – which had been previously significantly correlated with final YMRS and the HDRS (Hidalgo-Mazzei et al., 2016)- was not significant ($r=-0.20$, $p=0.94$). After controlling all these parameters with the final BRIAN scores with a multiple regression analysis, only the completion rates and the sleep time were able to significantly predict BRIAN scores ($F(2, 46) = 18.637$, $p < 0.001$) with an R^2 of 0.448).

Since variations of the BRIAN could be related not only to the intervention but also to medication adherence assessed through MG, we further explored this association. Final MG scores were positively correlated with the daily medication adherence question of the app ($r = 0.40$, $p = 0.01$), indicating a self-awareness of patients with the medication adherence. Due to the non-normal distribution of the final MG scores, a Wilcoxon signed-rank test was conducted, showing significant differences between MG pre and post scores ($Z = -2.86$, $p = 0.01$). Moreover, when categorizing these data according to adherence level, a McNemar-Bowker's test determined that there was a statistically significant difference in the proportion of adherence pre- and post-intervention ($p = 0.002$). However, including the MG final score as a covariate did not change the significant difference of the final BRIAN score between the group of completers and non-completers ($F = 1, 12$, $p = 0.001$) in a one-way ANCOVA in which previously a Levene's test and normality checks were again carried out and the assumptions met.

Discussion

Biological rhythms are key ingredients of most psychological interventions for BD and may play a different role in different phases of the therapy. Habits regularity is recommended by each and every guideline as a must in the prophylactic management of the illness and, of course, all BD psychological interventions have included "habits regularization" amongst their components (Reinares et al., 2014). Moreover, advice on habits is not only important in prophylaxis, but it is part of the non-pharmacological approach of oncoming episodes; i.e. in the case of early identifying a depressive episode, the therapist will suggest augmenting activation and limitation of sleeping time as a therapeutic advice whilst in the case of a "hype" the therapist usually will recommend cutting down the number of activities and augmenting time spent chilling out (Vieta et al., 2017). Undoubtedly, these recommendations would be less useful in the case of a full-blown episode but

are vital for aborting an episode which is about to start, once the patient is able to proceed with early identification of episodes. This is why all these recommendations are extremely common with psychoeducated patients (Colom and Vieta, 2006). And, it is worth noting, changes in habits regularity are usually the episode prodromes more commonly referred by patients during group psychoeducation, when they are asked to compose a list of early signs for every episode (Colom and Vieta, 2006).

Psychoeducation is, hence, able to help patients to change for good their habits. Cardoso and colleagues found an improvement in sleep and social domains of the BRIAN after 12-months in a group who received a brief group psychoeducation intervention on top of the usual care in comparison to those who only received usual care (Cardoso et al., 2014). In addition, the same authors reported an improvement in the quality of life in the psychoeducation group (Cardoso et al., 2014).

However, the worldwide availability of psychoeducation is still scarce (Colom, 2011). Many affected patients –probably a vast majority– will never have access to psychoeducation or similar therapies due to scarcity of trained therapists, costs, geographical availability and many other “real world” restrictions limiting treatment dissemination.

The growth of Internet-connected technologies opens new pathways to overcome these limitations (Emmelkamp, 2005; Glenn and Monteith, 2014; Hidalgo-Mazzei et al., 2015a), especially given the proven accuracy smartphone-based interventions when it comes to evaluate and potentially alter biological rhythms. In this regard, Murnane et al. found that smartphones usage in healthy controls is closely correlated to chronotype, alertness, and sleep (Murnane et al., 2016). Moreover, Runyan

et al. found that the use of smartphone applications improve self-awareness, which is widely suggested as a key positive behaviour change factor (Runyan et al., 2013). Similarly, but specifically addressing BD, Abdullah et al. evaluated the feasibility of inferring social rhythms in a sample of BD patients using automatically captured smartphone data. The authors found that solely relying on this kind of information it was possible to accurately predict social rhythm stability (Abdullah et al., 2016). Likewise, the Monitoring, Treatment and Prediction Of Bipolar Disorder Episodes (MONARCA) project has proved that combining both subjective and objective smartphone information could predict mood states (Faurholt-Jepsen et al., 2014). More recently, increasingly discrete and affordable wearables have shown to even enhance these capabilities, by continuously and accurately monitoring biological rhythms variables that may be crucial in BD such as sleep and physical activity (De Crescenzo et al., 2017; Geoffroy et al., 2015; Scott et al., 2017).

The present study shows positive effects of a psychoeducation-focused smartphone application as adjunctive to treatment as usual (TAU) in 4 out of 5 biological rhythms-related domains. When comparing pre and post BRIAN scores, SIMPLe showed efficacy at improving sleep, social rhythms, eating pattern and predominant rhythm. Changes regarding the “activities” domain also occurred as a trend, without reaching statistical significance, perhaps due to the limited sample size.

It should be noted that, being medication adherence modules another core component of psychoeducation, the medication adherence improvement alone could explain the biological rhythms difference between pre and post-intervention (Depp et al., 2008; Melo et al., 2016). Interestingly, Colom and colleagues reported increased regularity on lithium intake routines –and, hence, increased stability of serum lithium parameters- associated with psychoeducation (Colom et al., 2005a; Rahmani et al., 2016). Since in our results there was an improvement in both fields, the

fact that medication adherence helps habits regularization should not be entirely ruled out (Chatterton et al., 2017; Colom et al., 2005b; Wenzel et al., 2016). Similarly, we should not discard the opposite: the patient becoming more adherent by means of being more regular, as many medication intakes are linked to a very specific routine (i.e., taking the pills immediately before meals, or when brushing teeth, etc.). Even though, besides sleep and circadian rhythms, it is hard to link the medication adherence with other domains which have shown improvement, such as social and diet rhythms; these are commonly not directly related to pharmacological effects but instead to direct behavioural pattern changes. Indeed, in the present study the differences between completers and non-completers in the BRIAN total score remained significant after controlling the results by medication adherence.

The therapeutic advantages of improving biological rhythms and habits regularities through a simple and non-invasive device go beyond optimization of mood and avoidance of recurrences. As said, “regularly timed” patients may become more adherent (and, by being more adherent become even more regular, in a virtuous circle) and with the passing of time they will reduce the need of having a sedative compound prescribed. It has been described that subjects having a good sleep-wake regulation are also more prone to showing better cognitive performance, a phenomena probably mediated through adenosine (Reichert et al., 2016), so we may hypothesize on the importance of habits regularity to deal with neurocognitive problems associated to BD.

Another advantage of having a healthier chronotype has to do with the well-established link between biological rhythms and obesity (Gonissen et al., 2013), something to keep in mind considering that weight gain is a common –and difficult to treat- problem in people with BD and has also been related with a poor prognosis of the illness (Fagioli et al., 2003). Last, if we consider the

increase morbidity described for the bipolar population, it is remarkable the relationship between alterations in circadian rhythms and increased lipid peroxidation (which it's related to increased likelihood of Alzheimer disease and several types of cancer). This relationship exists in women suffering from BD but not in controls (Cudney et al., 2014). This suggests, again, a much-improved general health in "regularly timed" patients.

This is not the first study evaluating an Internet-based platform targeting components of biological rhythms in BD. Lieberman et al. tested the effect of a web-based mood and activities charting system -a key component of IPSRT- in the social rhythm of 64 BD patients during 3 months. They found a 31% increase in social rhythm stability and a significant decrease in symptoms (Lieberman et al., 2011). But in the mentioned study, the web seemed to work merely as a substitute of paper agenda, without using proper internet resources. In contrast, SIMPLe adds psychoeducational contents directly and dynamically targeting biological rhythm variations.

Nonetheless, some of the remaining questions that need to be solved regarding online interventions are the long-term engagement and the sustained effect of these approaches; especially, whether self-monitoring is modifying behaviour per se -as has been shown with other psychosocial interventions- or whether it is just a short-term Hawthorne like artefact (Colom et al., 2009; Depp et al., 2014; Hidalgo-Mazzei et al., 2015a; McCambridge et al., 2014; Torous et al., 2016). For instance, Depp et al. evaluated an add-on psychoeducation program using a mobile intervention. The authors reported an initial improvement at 6 and 8 months regarding depressive symptoms in the active group but unfortunately the effect did not remain significant after 24-months follow-up (Depp et al., 2014). However, there is still an ongoing discussion about the duration that these interventions should have, as well as the best methods to retain patients in long-term online interventions

(Morrison et al., 2012). In this regard, user-centered design (UCD) and gamification stand out among the new approaches suggested to improve engagement (McCurdie et al., 2012; Miller et al., 2014; Roth et al., 2014; Valimaki et al., 2008; van der Weegen et al., 2013).

Overall, taking into account the correlation of passive smartphone information data with social and circadian rhythms as well as the feasibility of delivering psychoeducational contents based on subjective information (Abdullah et al., 2016; Hidalgo-Mazzei et al., 2016), there is enough grounds to assume that these same devices could act as an external interactive biological rhythm pacemaker. Therefore, the use of the app seems to have contributed to regulating altered patterns in BD as it has been proved by the improvement of rhythms variables in comparison with users who stopped using the app. Future versions of the SIMPLE app (i.e. SIMPLE Plus) should be able to clarify some of these uncertainties, thanks to the possibilities to passively collect information from smartphone usage patterns and wearables alongside subjective information in order to tailor even more the psychoeducational contents. However, to definitely confirm the efficacy of this approach more research in the field is needed.

Limitations

It is worth mentioning that our results should be taken with caution due to some factors derived both from the smartphone app and the study. Intrinsic limitations of the app are described in detail somewhere else (Hidalgo-Mazzei et al., 2016). Regarding this particular study, it is important to note that analyses were conducted in a single group consisting of a consecutive sample of BD patients in a tertiary level reference centre. Additionally, it is worth mentioning that the small sample size does not allow the immediate generalization of the results in a wider and diverse population. Hence, this study may not represent the general population of BD patients at primary care facilities, and there is the possibility of having included individuals particularly motivated to use these devices. On the

other hand, the sample included in this study represents a real-world clinical population of BD patients.

Secondly, due to the design of the study, the analyses were mainly based on pre-post measures without an active control group, which limits the interpretation and emphasize the possibility of a Hawthorne or placebo effect (Torous et al., 2016). For the same reason, it is difficult to rule out the indirect influence in biological rhythms change due to changes in medication adherence despite the fact that we also controlled its role as a covariate. Furthermore, an increased baseline motivation in the use of new technologies among the completers group in comparison to non-completers could not be ruled out due to the lack of a randomization process.

Finally, due to time and resources constraints, the study was conducted during only three months, which is certainly a short time-frame to evaluate the long-term effects of any intervention; longer follow-up is ongoing.

Conclusion

The use of a smartphone application delivering personalized psychoeducational contents for BD, as an adjunct to TAU, has shown preliminary evidence of its capabilities to improve and regularize a key factor in the course of the disorder, as are biological rhythms. Despite the above-mentioned limitations, the results of the current study -together with the high feasibility that had been obtained with the use of the app (Hidalgo-Mazzei et al., 2016)- could pave the way for delivering in the near future a cost-effective tool to help regularize biological rhythms, and consequently improve the prognosis of this disorder as long as results of more long-term controlled trials become available.

Conflict of Interest

DH, AM, MR, EV and FC have designed the SIMPLe smartphone application mentioned in this study. The authors declare no other conflict of interests regarding this manuscript. The authors do not have any economic interests in the SIMPLe application, its use or copyrights.

Role of funding sources

This project was supported by research grants from the Spanish Ministry of Economy and Competitiveness PI14/00286 and PI15/00588, Instituto de Salud Carlos III, Subdirección General de Evaluación y Fomento de la Investigación; Fondo Europeo de Desarrollo Regional. Unión Europea, Una manera de hacer Europa (to DH and FC). Other sources of indirect support are a Río Hortega grant (CM15/00127) from Instituto de Salud Carlos III (to DH), a Beatriu de Pinós grant from Secretaria d'Universitats i Recerca del Departament d'Economia i Coneixement de la Generalitat de Catalunya i del programa COFUND de les Accions Marie Curie del 7è Programa marc de recerca i desenvolupament tecnològic de la Unió Europea (to MR), a research grant from the Spanish Ministry of Economy and Competitiveness (PI12/0091), Instituto de Salud Carlos III, Subdirección General de Evaluación y Fomento de la Investigación (to EV); by the Instituto de Salud Carlos III through the Centro para la Investigación Biomédica en Red de Salud Mental (CIBERSAM) as well as Secretaria d'Universitats i Recerca del Departament d'Economia i

Coneixement (2014_SGR_398).FC is funded by the Spanish Ministry of Economy and Competitiveness, Instituto de Salud Carlos III, through a Miguel Servet II postdoctoral contract and by a research grant from the Spanish Ministry of Economy and Competitiveness (PI 12/00910).

Authors' contribution

DH, MR, FC and EV participated in the initial study design. DH and MR were in charge of the patients recruitment and assessments. DH, AM and MJ performed the statistical analyses. MJ, MR and AY contributed to the interpretation of the results. DH and MJ drafted the first versions of the manuscripts, which was further reviewed and modified by AY, VP, EV and FC. All authors read and approved the final manuscript.

Acknowledgements

The authors would like to thank all the beta testers and users of the SIMPLe 1.0 application for their kind and permanent collaboration in this project. The technical development of the application software was commissioned to SODEP S.A. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. Similarly, the authors confirms that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional guides on the care and use of laboratory animals. The protocol of the project was approved in accordance to the local spanish laws (Ley orgánica de Protección de Datos de Carácter Personal (15/1999)). Additionally, the study

protocol was evaluated and approved (Reg. HCB/2014/0403) by the Hospital Clinic of Barcelona ethical committee and registered in ClinicalTrials.gov (Identifier: NCT02258711).

References

- Abdullah, S., Matthews, M., Frank, E., Doherty, G., Gay, G., Choudhury, T., 2016. Automatic detection of social rhythms in bipolar disorder. *J. Am. Med. Informatics Assoc.* 23, 538–543.
- American Psychiatric Association, 2013. *Diagnostic and Statistical Manual of Mental Disorders*, 5th Edition: DSM-5, 5th ed. American Psychiatric Publishing, Arlington, VA.
- Angst, F., Stassen, H.H., Clayton, P.J., Angst, J., 2002. Mortality of patients with mood disorders: follow-up over 34–38 years. *J. Affect. Disord.* 68, 167–81.
- Ashman, S.B., Monk, T.H., Kupfer, D.J., Clark, C.H., Myers, F.S., Frank, E., Leibenluft, 1999. Relationship between social rhythms and mood in patients with rapid cycling bipolar disorder. *Psychiatry Res.* 86, 1–8.
- Bauer, R., Conell, J., Glenn, T., Alda, M., Arda, R., Baune, B.T., Berk, M., Bersudsky, Y., Bilderbeck, A., Bocchetta, A., Bossini, L., Castro, A.M.P., Cheung, E.Y., Chillotti, C., Choppin, S., Del Zompo, M., Dias, R., Dodd, S., Duffy, A., Etain, B., Fagiolini, A., Hernandez, M.F., Garnham, J., Geddes, J.,

- Gildebro, J., Gonzalez-Pinto, A., Goodwin, G.M., Grof, P., Harima, H., Hassel, S., Henry, C., Hidalgo-Mazzei, D., Kapur, V., Kunigiri, G., Lafer, B., Larsen, E.R., Lewitzka, U., Licht, R.W., Lund, A.H., Misiak, B., Monteith, S., Munoz, R., Nakanotani, T., Nielsen, R.E., O'Donovan, C., Okamura, Y., Osher, Y., Piotrowski, P., Reif, A., Ritter, P., Rybakowski, J.K., Sagduyu, K., Sawchuk, B., Schwartz, E., Scippa, Â.M., Slaney, C., Sulaiman, A.H., Suominen, K., Suwalska, A., Tam, P., Tatebayashi, Y., Tondo, L., Vieta, E., Vinberg, M., Viswanath, B., Volkert, J., Zetin, M., Whybrow, P.C., Bauer, M., 2016. Internet use by patients with bipolar disorder: Results from an international multisite survey. *Psychiatry Res.* 242, 388–394.
- Cardoso, T. de A., Farias, C. de A., Mondin, T.C., da Silva, G.D.G., Souza, L.D. de M., da Silva, R.A., Pinheiro, K.T., do Amaral, R.G., Jansen, K., 2014. Brief psychoeducation for bipolar disorder: impact on quality of life in young adults in a 6-month follow-up of a randomized controlled trial. *Psychiatry Res.* 220, 896–902.
- Cardoso, T. de A., Mondin, T.C., Reyes, A.N., Zeni, C.P., Souza, L.D. de M., da Silva, R.A., Jansen, K., 2015. Biological Rhythm and Bipolar Disorder. *J. Nerv. Ment. Dis.* 203, 792–797.
- Chatterton, M. Lou, Stockings, E., Berk, M., Barendregt, J.J., Carter, R., Mihalopoulos, C., 2017. Psychosocial therapies for the adjunctive treatment of bipolar disorder in adults: network meta-analysis. *Br. J. Psychiatry* bjp.bp.116.195321.
- Colom, F., 2011. Keeping therapies simple: psychoeducation in the prevention of relapse in affective disorders. *Br. J. Psychiatry* 198, 338–40.
- Colom, F., Vieta, E., 2006. *Psychoeducation Manual for Bipolar Disorder*. CAMBRIDGE UNIVERSITY PRESS, Cambridge.
- Colom, F., Vieta, E., Martínez-Arán, A., Garcia-Garcia, M., Reinares, M., Torrent, C., Goikolea, J.M., Banús, S., Salamero, M., 2002. [Spanish version of a scale for the assessment of mania: validity and reliability of the Young Mania Rating Scale]. *Med. Clin. (Barc)*. 119, 366–71.

- Colom, F., Vieta, E., Sánchez-Moreno, J., Martínez-Arán, A., Reinares, M., Goikolea, J.M., Scott, J., 2005a. Stabilizing the stabilizer: group psychoeducation enhances the stability of serum lithium levels. *Bipolar Disord.* 7 Suppl 5, 32–6.
- Colom, F., Vieta, E., Sánchez-Moreno, J., Palomino-Otiniano, R., Reinares, M., Goikolea, J.M., Benabarre, A., Martínez-Arán, A., 2009. Group psychoeducation for stabilised bipolar disorders: 5-year outcome of a randomised clinical trial. *Br. J. Psychiatry* 194, 260–5.
- Colom, F., Vieta, E., Tacchi, M., Sanchez-Moreno, J., Scott, J., 2005b. Identifying and improving non-adherence in bipolar disorders. *Bipolar Disord.* 7, 24–31.
- Cudney, L.E., Sassi, R.B., Behr, G.A., Streiner, D.L., Minuzzi, L., Moreira, J.C.F., Frey, B.N., 2014. Alterations in circadian rhythms are associated with increased lipid peroxidation in females with bipolar disorder. *Int. J. Neuropsychopharmacol.* 17, 715–722.
- De Crescenzo, F., Economou, A., Sharpley, A.L., Gormez, A., Quedsted, D.J., 2017. Actigraphic features of bipolar disorder: A systematic review and meta-analysis. *Sleep Med. Rev.* 33, 58–69.
- Depp, C.A., Ceglowski, J., Wang, V.C., Yaghouti, F., Mausbach, B.T., Thompson, W.K., Granholm, E.L., 2014. Augmenting psychoeducation with a mobile intervention for bipolar disorder: A randomized controlled trial. *J. Affect. Disord.* 174C, 23–30.
- Depp, C.A., Moore, D.J., Patterson, T.L., Lebowitz, B.D., Jeste, D. V, 2008. Psychosocial interventions and medication adherence in bipolar disorder. *Dialogues Clin. Neurosci.* 10, 239–50.
- Emmelkamp, P.M.G., 2005. Technological innovations in clinical assessment and psychotherapy. *Psychother. Psychosom.* 74, 336–43.
- Fagiolini, A., Kupfer, D.J., Houck, P.R., Novick, D.M., Frank, E., 2003. Obesity as a correlate of outcome in patients with bipolar I disorder. *Am. J. Psychiatry* 160, 112–7.
- Faurholt-Jepsen, M., Frost, M., Vinberg, M., Christensen, E.M., Bardram, J.E., Kessing, L.V., 2014.

- Smartphone data as objective measures of bipolar disorder symptoms. *Psychiatry Res.* 217, 124–7.
- Frank, E., 2007. Interpersonal and social rhythm therapy: A means of improving depression and preventing relapse in bipolar disorder. *J. Clin. Psychol.* 63, 463–473.
- Frank, E., Kupfer, D.J., Thase, M.E., Mallinger, A.G., Swartz, H.A., Fagiolini, A.M., Grochocinski, V., Houck, P., Scott, J., Thompson, W., Monk, T., 2005. Two-Year Outcomes for Interpersonal and Social Rhythm Therapy in Individuals With Bipolar I Disorder. *Arch. Gen. Psychiatry* 62, 996.
- Geoffroy, P.A., Scott, J., Boudebessé, C., Lajnef, M., Henry, C., Leboyer, M., Bellivier, F., Etain, B., 2015. Sleep in patients with remitted bipolar disorders: a meta-analysis of actigraphy studies. *Acta Psychiatr. Scand.* 131, 89–99.
- Gershon, A., Ram, N., Johnson, S.L., Harvey, A.G., Zeitzer, J.M., 2016. Daily Actigraphy Profiles Distinguish Depressive and Interepisode States in Bipolar Disorder. *Clin. Psychol. Sci.* 4, 641–650.
- Giglio, L.M., Magalhães, P.V.S.S., Kapczinski, N.S., Walz, J.C., Kapczinski, F., 2010. Functional impact of biological rhythm disturbance in bipolar disorder. *J. Psychiatr. Res.* 44, 220–3.
- Giglio, L.M.F., Magalhães, P.V. da S., Andreazza, A.C., Walz, J.C., Jakobson, L., Rucci, P., Rosa, A.R., Hidalgo, M.P., Vieta, E., Kapczinski, F., 2009. Development and use of a biological rhythm interview. *J. Affect. Disord.* 118, 161–5.
- Glenn, T., Monteith, S., 2014. New measures of mental state and behavior based on data collected from sensors, smartphones, and the Internet. *Curr. Psychiatry Rep.* 16, 523.
- Gonnissen, H.K.J., Hulshof, T., Westerterp-Plantenga, M.S., 2013. Chronobiology, endocrinology, and energy- and food-reward homeostasis. *Obes. Rev.* 14, 405–416.
- Grande, I., Berk, M., Birmaher, B., Vieta, E., 2016. Bipolar disorder. *Lancet* 387, 1561–1572.

Hamilton, M., 1960. A rating scale for depression. *J. Neurol. Neurosurg. Psychiatry* 23, 56–62.

Harvey, A.G., Talbot, L.S., Gershon, A., 2009. Sleep Disturbance in Bipolar Disorder Across the Lifespan. *Clin. Psychol. (New York)*. 16, 256–277.

Haynes, P.L., Gengler, D., Kelly, M., 2016. Social Rhythm Therapies for Mood Disorders: an Update. *Curr. Psychiatry Rep.* 18, 75.

Hidalgo-Mazzei, D., Mateu, A., Reinares, M., Matic, A., Vieta, E., Colom, F., 2015a. Internet-based psychological interventions for bipolar disorder: Review of the present and insights into the future. *J. Affect. Disord.* 188, 1–13.

Hidalgo-Mazzei, D., Mateu, A., Reinares, M., Murru, A., Del Mar Bonnín, C., Varo, C., Valentí, M., Undurraga, J., Strejilevich, S., Sánchez-Moreno, J., Vieta, E., Colom, F., 2016. Psychoeducation in bipolar disorder with a SIMPLe smartphone application: Feasibility, acceptability and satisfaction. *J. Affect. Disord.* 200, 58–66.

Hidalgo-Mazzei, D., Mateu, A., Reinares, M.M., Undurraga, J., Bonnín, C. del M., Sánchez-Moreno, J., Vieta, E., Colom, F., Undurraga, J., Bonnín, C. del M., Sánchez-Moreno, J., Vieta, E., Colom, F., 2015b. Self-monitoring and psychoeducation in bipolar patients with a smart-phone application (SIMPLe) project: design, development and studies protocols. *BMC Psychiatry* 15, 52.

Kessing, L.V., Vradi, E., Andersen, P.K., 2015. Life expectancy in bipolar disorder. *Bipolar Disord.* 17, 543–548.

Lieberman, D.Z., Swayze, S., Goodwin, F.K., 2011. An automated Internet application to help patients with bipolar disorder track social rhythm stabilization. *Psychiatr. Serv.* 62, 1267–9.

Martínez-Arán, A., Vieta, E., Reinares, M., Colom, F., Torrent, C., Sánchez-Moreno, J., Benabarre, A., Goikolea, J.M., Comes, M., Salamero, M., 2004. Cognitive function across manic or hypomanic, depressed, and euthymic states in bipolar disorder. *Am. J. Psychiatry* 161, 262–70.

- McCambridge, J., Witton, J., Elbourne, D.R., 2014. Systematic review of the Hawthorne effect: new concepts are needed to study research participation effects. *J. Clin. Epidemiol.* 67, 267–77.
- McCurdie, T., Taneva, S., Casselman, M., Yeung, M., McDaniel, C., Ho, W., Cafazzo, J., 2012. mHealth consumer apps: the case for user-centered design. *Biomed. Instrum. Technol. Suppl.* 49–56.
- Melo, M.C.A., Abreu, R.L.C., Linhares Neto, V.B., de Bruin, P.F.C., de Bruin, V.M.S., 2016. Chronotype and circadian rhythm in bipolar disorder: A systematic review. *Sleep Med. Rev.* 16, S1087-792.
- Merikangas, K.R., Jin, R., He, J.-P., Kessler, R.C., Lee, S., Sampson, N.A., Viana, M.C., Andrade, L.H., Hu, C., Karam, E.G., Ladea, M., Medina-Mora, M.E., Ono, Y., Posada-Villa, J., Sagar, R., Wells, J.E., Zarkov, Z., 2011. Prevalence and correlates of bipolar spectrum disorder in the world mental health survey initiative. *Arch. Gen. Psychiatry* 68, 241–51.
- Michalak, E.E., Yatham, L.N., Lam, R.W., 2005. Quality of life in bipolar disorder: a review of the literature. *Health Qual. Life Outcomes* 3, 72.
- Miller, A.S., Cafazzo, J.A., Seto, E., 2014. A game plan: Gamification design principles in mHealth applications for chronic disease management. *Health Informatics J.*
- Morahan-Martin, J., Schumacher, P., 2003. Loneliness and social uses of the Internet. *Comput. Human Behav.* 19, 659–671.
- Morisky, D.E., Green, L.W., Levine, D.M., 1986. Concurrent and predictive validity of a self-reported measure of medication adherence. *Med. Care* 24, 67–74.
- Moro, M.F., Carta, M.G., Pintus, M., Pintus, E., Melis, R., Kapczinski, F., Vieta, E., June, F.C., 2014. Validation of the Italian Version of the Biological Rhythms Interview of Assessment in Neuropsychiatry (BRIAN): Some Considerations on its Screening Usefulness. *Clin. Pract. Epidemiol. Ment. Heal.* 10, 48–52.
- Morrison, L.G., Yardley, L., Powell, J., Michie, S., 2012. What Design Features Are Used in Effective e-

Health Interventions? A Review Using Techniques from Critical Interpretive Synthesis. *Telemed. e-Health* 18, 137–144.

Murnane, E.L., Abdullah, S., Matthews, M., Kay, M., Kientz, J.A., Choudhury, T., Gay, G., Cosley, D., 2016. Mobile manifestations of alertness, in: *Proceedings of the 18th International Conference on Human-Computer Interaction with Mobile Devices and Services - MobileHCI '16*. ACM Press, New York, New York, USA, pp. 465–477.

Murray, G., Harvey, A., 2010. Circadian rhythms and sleep in bipolar disorder. *Bipolar Disord.* 12, 459–472.

Pinho, M., Sehmbi, M., Cudney, L.E., Kauer-Sant'anna, M., Magalhães, P. V., Reinares, M., Bonnín, C.M., Sassi, R.B., Kapczinski, F., Colom, F., Vieta, E., Frey, B.N., Rosa, A.R., 2016. The association between biological rhythms, depression, and functioning in bipolar disorder: a large multi-center study. *Acta Psychiatr. Scand.* 133, 102–108.

Rahmani, F., Ebrahimi, H., Ranjbar, F., Razavi, S.S., Asghari, E., 2016. The Effect of Group Psychoeducation Program on Medication Adherence in Patients with Bipolar Mood Disorders: a Randomized Controlled Trial. *J. caring Sci.* 5, 287–297.

Ramos-Brieva, J.A., Cordero-Villafañila, A., 1988. A new validation of the Hamilton Rating Scale for Depression. *J. Psychiatr. Res.* 22, 21–8.

Reichert, C.F., Maire, M., Schmidt, C., Cajochen, C., 2016. Sleep-Wake Regulation and Its Impact on Working Memory Performance: The Role of Adenosine. *Biology (Basel)*. 5, 11.

Reinares, M., Sánchez-Moreno, J., Fountoulakis, K.N., 2014. Psychosocial interventions in bipolar disorder: what, for whom, and when. *J. Affect. Disord.* 156, 46–55.

Rosa, A.R., Comes, M., Torrent, C., Solè, B., Reinares, M., Pachiarotti, I., Salamero, M., Kapczinski, F., Colom, F., Vieta, E., 2013. Biological rhythm disturbance in remitted bipolar patients. *Int. J.*

- Roth, W.R., Vilardaga, R., Wolfe, N., Bricker, J.B., McDonell, M.G., 2014. Practical considerations in the design and development of smartphone apps for behavior change. *J. Context. Behav. Sci.* 3, 269–272.
- Runyan, J.D., Steenbergh, T.A., Bainbridge, C., Daugherty, D.A., Oke, L., Fry, B.N., 2013. A Smartphone Ecological Momentary Assessment/Intervention “App” for Collecting Real-Time Data and Promoting Self-Awareness. *PLoS One* 8, e71325.
- Sarwar, M., Rahim Soomro, T., 2013. Impact of Smartphone’s on Society. *Eur. J. Sci. Res.* 98, 216–226.
- Scott, J., Vaaler, A.E., Fasmer, O.B., Morken, G., Krane-Gartiser, K., 2017. A pilot study to determine whether combinations of objectively measured activity parameters can be used to differentiate between mixed states, mania, and bipolar depression. *Int. J. Bipolar Disord.* 5, 5.
- Shen, G.H.C., Sylvia, L.G., Alloy, L.B., Barrett, F., Kohner, M., Iacoviello, B., Mills, A., 2008. Lifestyle regularity and cyclothymic symptomatology. *J. Clin. Psychol.* 64, 482–500.
- Stafford, N., Colom, F., 2013. Purpose and effectiveness of psychoeducation in patients with bipolar disorder in a bipolar clinic setting. *Acta Psychiatr. Scand. Suppl.* 11–8.
- Torous, J., Firth, J., Vettorazzi, E., al., et, Bricker, J., 2016. The digital placebo effect: mobile mental health meets clinical psychiatry. *The Lancet Psychiatry* 3, 100–102.
- Valimaki, M., Anttila, M., Hatonen, H., Koivunen, M., Jakobsson, T., Pitkanen, A., Herrala, J., Kuosmanen, L., 2008. Design and development process of patient-centered computer-based support system for patients with schizophrenia spectrum psychosis. *Inform. Health Soc. Care* 33, 113–23.
- van der Weegen, S., Verwey, R., Spreeuwenberg, M., Tange, H., van der Weijden, T., de Witte, L.,

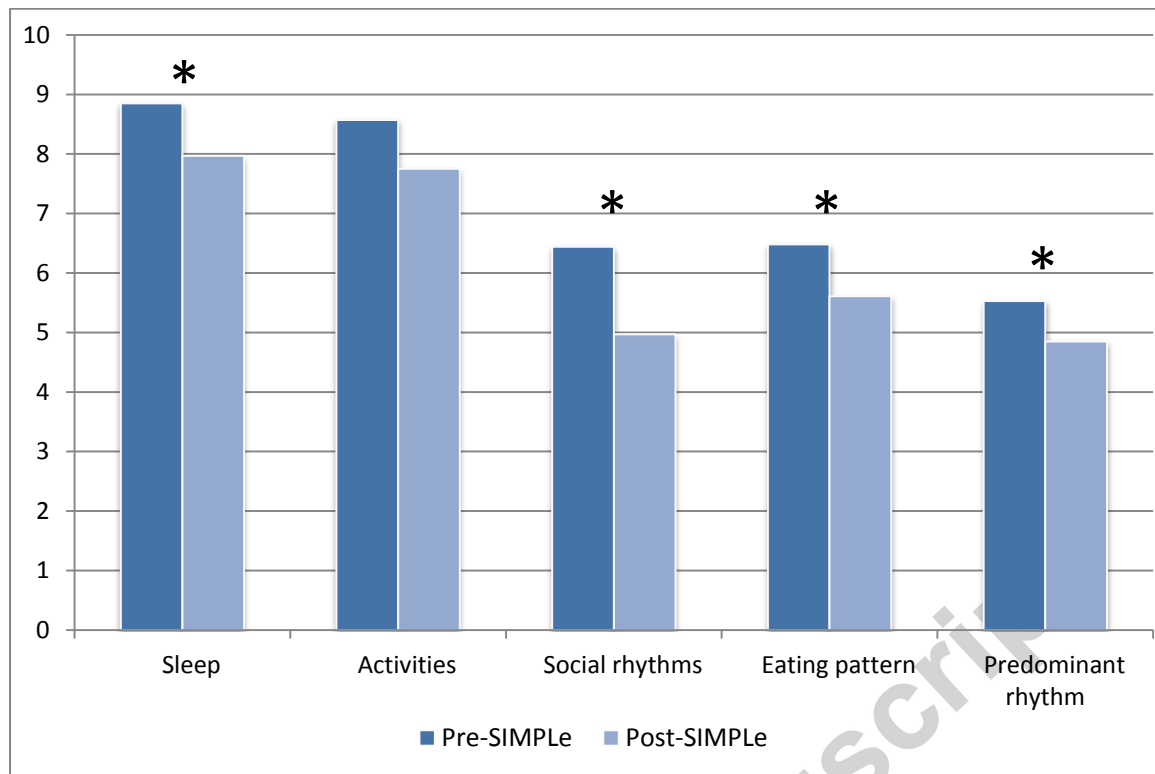
2013. The development of a mobile monitoring and feedback tool to stimulate physical activity of people with a chronic disease in primary care: a user-centered design. *JMIR mHealth uHealth* 1, e8.

Vieta, E., Sanchez-Moreno, J., Spineli, L., al., et, 2017. Behavioural activation training for depression. *Lancet* (London, England) 389, 367.

Wenze, S.J., Armey, M.F., Weinstock, L.M., Gaudiano, B.A., Miller, I.W., 2016. An Open Trial of a Smartphone-assisted, Adjunctive Intervention to Improve Treatment Adherence in Bipolar Disorder. *J. Psychiatr. Pract.* 22, 492–504.

Young, R.C., Biggs, J.T., Ziegler, V.E., Meyer, D.A., 1978. A rating scale for mania: reliability, validity and sensitivity. *Br. J. Psychiatry* 133, 429–35.

Figure 1. BRIAN subdomains before and after the intervention



The figure shows the variations of each domain of the BRIAN score before and after the use of the SIMPLE 1.0 app. The asterisk (*) marks those subdomains in which variations were statistically significant ($p < 0.05$).

Table 1. BRIAN Subdomains before and after the intervention

BRIAN subdomains	pre-SIMPLE		post-SIMPLE		t value*	p value
	Mean	SD	Mean	SD		
<i>Sleep</i>	8.85	2.39	7.97	2.07	2.34	0.023
<i>Activities</i>	8.57	2.54	7.75	2.41	1.85	0.071
<i>Social rhythms</i>	6.44	1.87	4.97	1.5	4.94	0.001
<i>Eating pattern</i>	6.48	2.2	5.61	1.74	2.81	0.007
<i>Predominant rhythm</i>	5.53	1.19	4.85	1.39	3.39	0.001
Total BRIAN	35.89	6.64	31.18	6.33	4.29	0.001

* *Paired t-test*

BRIAN = Biological Rhythms Interview of Assessment in Neuropsychiatry

Table 2. Baseline sociodemographic and clinical characteristics divided in groups of non-completers and completers

		Non-completers (N = 13)		Completers (N = 36)	
		Mean	SD	Mean	SD
Age		41	9	45	12
YMRS		3.46	3.64	1.67	2.03
HDRS		2.54	2.79	3.42	2.67
FAST		6.54	10.67	15.11	12.18
MG		0.54	0.66	0.53	0.7
Illness duration		13.08	8.1	12.56	10.11
Number of previous episodes		6.08	3.66	5.22	2.76
Predominant Polarity		1.67	1.17	1.24	0.74
		N	%	N	%
Gender	<i>Male</i>	8	61.5%	20	55.6%
	<i>Female</i>	5	38.5%	16	44.4%
Marital status	<i>Single</i>	6	46.2%	16	44.4%
	<i>Married</i>	6	46.2%	14	38.9%
	<i>Divorced / Separated</i>	1	7.7%	6	16.7%
Education	<i>Primary</i>	1	7.7%	2	5.6%
	<i>High</i>	2	15.4%	14	38.9%
	<i>Technical degree</i>	4	30.8%	6	16.7%
	<i>University degree</i>	6	46.2%	14	38.9%
Employment status	<i>Unemployed</i>	1	7.7%	3	8.3%
	<i>Employed</i>	7	53.8%	14	38.9%
	<i>Retired</i>	0	0.0%	4	11.1%
	<i>Incapacitated</i>	5	38.5%	15	41.7%
Family psychiatric history	<i>1st degree</i>	7	53.8%	19	52.8%
	<i>2nd degree</i>	1	7.7%	8	22.2%
	<i>3rd degree</i>	0	0.0%	2	5.6%
Type of Bipolar Disorder	<i>I</i>	11	84.6%	22	61.1%
	<i>II</i>	2	15.4%	11	30.6%
	<i>NES</i>	0	0.0%	3	8.3%
SUD comorbidity		7	53.8%	10	27.8%

PD comorbidity	2	15.4%	4	11.1%
Medical comorbidity	4	30.8%	16	44.4%

YMRS = Young Mania rating score, HDRS = 17 item Hamilton depression rating scale, MG= 4-item Morisky-Green score, FAST = Functioning Assessment Short Test, PD= Personality disorder, SUD = Substance use disorder, NES = Not elsewhere specified.

Table 3. Clinical variables variations before and after the intervention

Clinical variables	Pre-SIMPLE		Post-SIMPLE		t value	p value
	Mean	SD	Mean	SD		
YMRS	2.14	2.63	1.51	3.61	0.954	0.345
HDRS	3.18	2.69	3.76	4.97	-0.712	0.48
MG	35.90	6.64	31.18	6.33	-3.31*	0.001
	N	%	N	%		
MG Categories						
Low	5	10.2	1	2		
Moderate	20	40.8	11	22.4	13.0**	0.002
High	24	49	37	75.5		

* Z Wilcoxon Signed Ranks Test value

** McNemar-Bowker test

YMRS = Young Mania rating score, HDRS = 17 item Hamilton depression rating scale, MG= 4-item Morisky Green score.

Highlights

- Biological rhythms play a crucial role in the course and functioning of BD patients.
- Most psychological interventions for BD target habits regularity to normalize them.
- Smartphones' data has a close correlation with biological rhythms.
- SIMPLE is a smartphone application delivering psychoeducational contents for BD.
- It has shown preliminary evidence of its capabilities to improve biological rhythms.